The role of fourth-generation cephalosporins in the treatment of infections caused by penicillin-resistant streptococci

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The incidence of penicillin resistance amongst *Streptococcus pneumoniae* is increasing on a world-wide basis. Penicillin-resistant strains of viridans streptococci have also been reported, associated with serious clinical infections, particularly in neutropenic patients. Although there are fewer data on the epidemiology of viridans streptococci, it is known that penicillin resistance determinants can be transferred between these organisms and *S. pneumoniae*. Paradoxically, the increased incidence of multiresistant pneumococci has led to a re-evaluation of β-lactam antibiotics for the treatment of streptococcal infections.

Cefotaxime, ceftriaxone, cefpirome, cefepime, imipenem, meropenem and amoxicillin remain the most potent β-lactam antibiotics, with at least 95% of penicillin-resistant strains of *S. pneumoniae* being inhibited by 2 mg/L and 95% of penicillin-resistant viridans streptococci by 8 mg/L. Cefpirome is two-fold more active than cefotaxime, ceftriaxone or cefepime and, like penicillin and cefotaxime, is bactericidal at 2x and 4x the MIC value against penicillin-resistant strains of *S. pneumoniae* and viridans streptococci. Synergistic interactions have been demonstrated between penicillin or cefpirome and vancomycin, fosfomycin or gentamicin.

Studies have shown that the clinical outcome of pneumonia is not related to in vitro MIC data below 4 mg/L, since infections caused by penicillin-resistant pneumococci responded as well to β-lactam therapy as those caused by penicillin-susceptible strains. This is most likely to be due to high antibiotic concentrations achieved at the site of infection following intravenous dosage, which are sufficient to cover strains with reduced susceptibility. Any degree of penicillin resistance rules out the use of penicillin for pneumococcal meningitis, necessitating the use of extended-spectrum cephalosporins, such as cefotaxime or ceftriaxone. An alternative could be the use of the fourth-generation cephalosporins or the carbapenems. Overall, when predicting the clinical outcome of infections caused by penicillin-resistant streptococci, it is important to consider the relationship between a number of factors, namely, the specific susceptibility of the infecting strain to the chosen agent, the type of infection (i.e. pneumonia, bacteremia or meningitis) and the relevant antibiotic concentrations achieved over time at the site of infection (i.e. those in serum or cerebrospinal fluid).

Key words: *Streptococcus pneumoniae*, viridans streptococci, penicillin resistance, epidemiology, cephalosporins, cefpirome

INTRODUCTION

Streptococcus pneumoniae is a major bacterial pathogen responsible for respiratory tract infections, including community-acquired and nosocomial pneumonia. It is also the most important bacterial pathogen causing meningitis and acute otitis media, and the increasing incidence of antibiotic-resistant strains has made the treatment of these infections a difficult and controversial topic. The first penicillin-resistant strain of *S. pneumoniae* was reported in 1967 [1] and, since then, the incidence of penicillin resistance has increased dramatically world-wide. A number of countries, including Spain [2], Hungary [3] and South Africa [4], have a particularly high prevalence of penicillin-resistant pneumococci (44–59%), as well as France (40–45%), which may be related to patterns of antibiotic usage in these areas [3,5,6]. There is also some evidence that penicillin-resistant clones of

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S. pneumoniae belonging to serotype 6B and 23F have been exported from these countries to others, for example, from Spain to Iceland [7], France [8], South Africa [9] and the United States [10], and these have been tracked by molecular analysis of the strains. Other serotypes, such as 19B, are prevalent in countries such as Japan [11,12].

Although viridans-group streptococci, comprising the species *S. mitis, S. sanguis, S. anginosus* and *S. salivarius*, have long been known to cause endocarditis, they were previously regarded as minor pathogens in other clinical settings. They have now become a prominent cause of bacteremia in neutropenic patients [13,14]. Penicillin-resistant strains of viridans streptococci have been known since 1962 [15–17].

Many penicillin-resistant strains of streptococci, particularly the highly penicillin-resistant strains, are also resistant to other antibiotics [5,6,18] such as macrolides, tetracyclines, co-trimoxazole and chloramphenicol. Since agents such as the currently available quinolones are generally not highly potent against streptococci, the therapeutic options for serious infections caused by these organisms are limited.

The β-hemolytic streptococci (groups A, B, C and G) cause 3.3% of bloodstream infections [19]. The virulence of this group of organisms, and consequent high morbidity or mortality in even previously healthy subjects, gives β-hemolytic streptococci clinical significance [20]. During the last few years, there has been an increase in the number of reports of serious infections caused by group A streptococci including bacteremia, toxic shock and necrotising fasciitis. These streptococci have become increasingly important because of modified virulence of *S. pyogenes* strains [19]. Strains of *S. pyogenes* are increasingly resistant to the macrolides [20] and there is a fear that they may also develop resistance to penicillin and other β-lactam antibiotics.

EPIDEMIOLOGY

The epidemiology of pneumococcal resistance has changed over the last few years and has spread to countries with previously low levels of resistance [21]. High level penicillin resistance for *S. pneumoniae* is defined as a minimum inhibitory concentration (MIC) ≥ 2 mg/L, intermediate penicillin resistance as an MIC of 0.12–1 mg/L and susceptibility as an MIC of ≤ 0.06 mg/L. Figure 1 shows the current situation regarding resistance to penicillin amongst *S. pneumoniae* strains isolated from approximately 200 centers, mainly between 1993 and 1996 [Klugman and Baquero, review of published and unpublished data]. Penicillin resistance is defined here and in Figure 1, as an MIC value greater than 0.12 mg/L and, therefore, includes both intermediate and high-level penicillin-resistant strains.

Resistant pneumococci were commonly isolated in South Africa, Spain, Papua New Guinea and Eastern Europe in the early 1980s. However, other countries, such as France, Argentina, Uruguay, Mexico, Israel, Saudi Arabia, Nigeria, Kenya and Japan are currently reporting incidences of > 40%. Recent data available from Korea shows a very high incidence of > 60%, although many of these strains are nosocomially-acquired. Ninety-five percent of nosocomially-acquired pneumococcal bacteremias at the Baragwanath Hospital, Soweto are penicillin-resistant [22]. Rates of 20–30% are reported in countries such as Turkey, Venezuela, Brazil and Chile and in most states in the USA [23]. In contrast, low levels of resistance are reported in most northern European countries, Greece and Italy. Rates of 5, 27 and 10% have been reported from Moscow, Smolensk and St. Petersburg respectively, but more data are needed from Russia.

The maximum levels of resistance are currently a penicillin MIC of 8 mg/L, reported for strains of *S. pneumoniae* in France [6] and Spain, and 16 mg/L in Hungary [24]. Penicillin-resistant *S. pneumoniae* are isolated at a greater frequency from hospitalized children, children in day-care centers and those previously exposed to antibiotics, particularly those with acute otitis media. These factors may explain local discrepancies with very high incidences of penicillin-resistant strains [6].

Since 1983, there have been several reports disclosing high level penicillin resistance among viridans streptococci isolated from clinically significant infections [15–17]. For viridans streptococci, high level penicillin resistance is defined as an MIC of ≥ 4 mg/L, intermediate resistance as 0.25–2 mg/L and susceptiblility as < 0.25 mg/L [25]. In recent studies in the USA, only 44–49% of viridans streptococci isolated from blood were susceptible to penicillin [19,26,27]. The US data are similar to South African figures of 42–67% susceptibility [17], whereas data from Switzerland (1988–1991) indicate that 15% of strains are penicillin-resistant [28]. Among the South African strains, 8% had penicillin MIC values ≥ 4 mg/L, as had 13.4% of strains from the USA [26]. Strains with similar levels of resistance have been reported in Europe [28].

MOLECULAR BASIS OF RESISTANCE

The target sites for β-lactam antibiotics are the penicillin-binding proteins (PBPs). Resistance is mediated by molecular changes which occur within the PBPs [16,29,30] (Table 1), which confer reduced

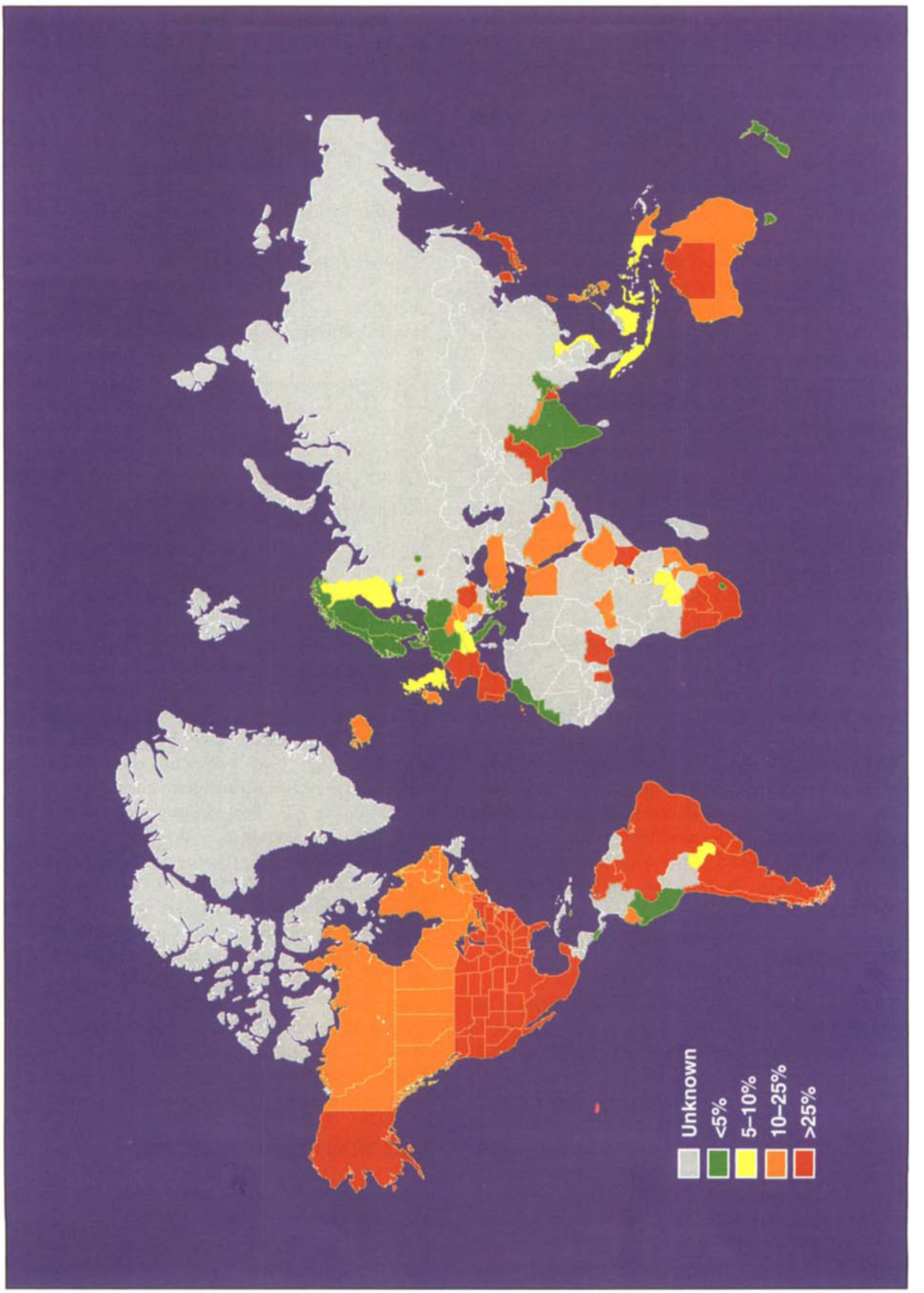

Figure 1 Worldwide frequency of isolation of penicillin-resistant pneumococci (MIC > 0.12 mg/L, intermediate and high-level penicillin-resistant strains).

Table 1 Penicillin-binding proteins (PBPs) modified to give different penicillin and cephalosporin resistance phenotypes in streptococci

Phenotype		
Penicillin susceptibility	Cephalosporin susceptibility	PBPs modified
Sensitive	Sensitive	$1a^N$, $2x^N$, $2b^N$
Very low level resistance	Sensitive	$1a^N$, $2x^P$, $2b^N$
Intermediate	Sensitive	$1a^P$, $2x^P$, $2b^N$
Resistant	Sensitive	$1a^P$, $2x^P$, $2b^P$
Intermediate	Resistant	$1a^{PC}$, $2x^{PC}$, $2b^N$
Resistant	Resistant	$1a^{PC}$, $2x^{PC}$, $2b^P$

N = Normal PBP.
P = PBP mutated to give reduced susceptibility to penicillin.
C = PBP mutated to give cephalosporin resistance.

susceptibility to all β-lactam antibiotics to a greater or lesser extent [31]. Wild-type strains with a very low or intermediate level of resistance to penicillin possess mutations in PBP 2x, and when a modification in PBP 2b is added, a change from intermediate resistance to high-level penicillin resistance occurs [32]. Sequential mutations in the gene encoding a penicillin-susceptible PBP 2b can also occur, each of which further increases the level of resistance to penicillin. Acquisition of blocks of DNA to make up a mosaic pattern of DNA, encoding resistant parts of the protein, is the hallmark of the changes in the PBP genes. The 'resistant' blocks are acquired by homologous recombination in these naturally transformable organisms [33].

A specific alteration at position 550 of PBP 2x, in the presence of altered PBP 1a, results in high-level cephalosporin resistance, but with an intermediate level of resistance to penicillins [34]. Multiresistance to both penicillins and cephalosporins, which occurs frequently, caused by double mutations in PBPs 1a and 2x, decreasing the susceptibility to both classes, as well as mutations in PBP 2b, giving high-level penicillin-resistance. There is evidence that the altered PBPs in viridans group streptococci have been obtained by gene transfer from *S. pneumoniae* and vice versa [30,35].

IN VITRO SUSCEPTIBILITY

Minimum inhibitory concentrations

The increasing prevalence of penicillin-resistant *S. pneumoniae* throughout the world means that there is a need for antibiotics with potent activity against these organisms. A recent multicenter study, conducted in Spain, has compared the activity of third- and fourth-generation cephalosporins and the carbapenem, imipenem, against penicillin-susceptible, penicillin-intermediate and penicillin-resistant *S. pneumoniae* (Table 2) [36]. The current NCCLS susceptibility breakpoints for the cephalosporins, recommended for *S. pneumoniae* infections are: susceptible, ≤ 0.5 mg/L, intermediate resistance, 1.0 mg/L and resistant, ≥ 2 mg/L. Against penicillin-intermediate strains, cefpirome, cefotaxime (or ceftriaxone, data not shown) were the most active compounds, with MIC_{90} values of 0.5 mg/L, with cefepime being slightly less active (MIC_{90} value, 1.0 mg/L).

Against penicillin-resistant strains, cefpirome and imipenem were the most active compounds overall, with maximum MICs of 1.0 mg/L. Cefepime and cefotaxime (or ceftriaxone) were two-fold less active and although the difference in MIC values was only small, this may be important in the treatment of infections, particularly when considering the antibiotic levels which are likely to be achieved at the site of infection in cases of meningitis.

Other studies have confirmed a two-fold advantage in the in vitro activity of cefpirome against *S. pneumoniae* compared to cefepime, cefotaxime and ceftriaxone [31,37,38], and data from South Africa (Table 3) also show cefotaxime and ceftriaxone to be two-fold less active than cefpirome, whereas cefepime was four-fold less active than cefpirome against both penicillin-intermediate and penicillin-resistant pneumococci. The South African strains examined were generally less susceptible than that of the Spanish strains, with the MIC_{90} values against the penicillin-resistant strains being 4 mg/L for penicillin, cefepime and cefodizime, and 2 mg/L for cefotaxime and ceftriaxone. The MIC_{90} value of cefpirome, however, was 1.0 mg/L, the same as for the Spanish strains.

Ceftazidime was much less active than penicillin

Table 2 Susceptibility of strains of *S. pneumoniae* from Spain to six β-lactam antibiotics

Category	Antibiotic	MIC (mg/L)		
		50%	90%	Range
Penicillin-susceptible	ceftazidime[a]	0.12	0.25	0.06–0.25
(MIC ≤ 0.06 mg/L)	cefepime	0.015	0.03	0.008–0.12
n = 100	cefpirome	0.03	0.03	0.008–0.06
	cefotaxime[b]	0.03	0.03	0.008–0.03
	imipenem	0.008	0.008	0.008–0.03
Penicillin-intermediate	ceftazidime[a]	4	8	0.5–16
(MIC 0.12–1.0 mg/L)	cefepime	0.5	1.0	0.008–1.0
n = 100	cefpirome	0.25	0.5	0.008–1.0
	cefotaxime[b]	0.25	0.5	0.008–1.0
	imipenem	0.06	0.12	0.008–0.25
Penicillin-resistant	ceftazidime[a]	16	>32	16–64
(MIC ≥ 2 mg/L)	cefepime	1.0	1.0	0.12–2
n = 100	cefpirome	0.5	1.0	0.12–1.0
	cefotaxime[b]	0.5	1.0	0.06–2
	imipenem	0.25	0.5	0.06–1.0

[a]Ceftizoxime showed similar activity to ceftazidime.
[b]Ceftriaxone showed comparable activity to cefotaxime.
Adapted from Martínez-Beltrán et al. [36].

Table 3 Susceptibility of South African strains of *S. pneumoniae* to six β-lactam antibiotics

Antibiotic	MIC_{90} (mg/L)[a]		
	Penicillin-susceptible (*n* = 65)	Penicillin-intermediate (*n* = 85)	Penicillin-resistant (*n* = 60)
Penicillin	0.06	1.0	4
Ceftazidime	1.0	16	64
Cefepime	0.12	2	4
Cefpirome	0.12	0.5	1.0
Cefotaxime	0.06	1.0	2
Ceftriaxone	0.06	1.0	2
Cefodizime	0.12	4	4

[a]MIC determinations were performed according to NCCLS criteria using the microdilution method.

or the other cephalosporins tested, with MIC_{90} values for penicillin-intermediate and penicillin-resistant strains of 8–16 mg/L and 64 mg/L, respectively (Tables 2 and 3). The activity of ceftizoxime has been found to be similar to ceftazidime and lower than ceftriaxone and cefotaxime against penicillin-intermediate and penicillin-resistant pneumococci [31]. Although imipenem was consistently the most active compound tested, meropenem has been shown to be two-fold less active than imipenem [31], but more active than cefotaxime or ceftriaxone. Amoxicillin has also shown similar activity to cefotaxime and ceftriaxone against penicillin-intermediate and penicillin-resistant pneumococci [18,31].

Penicillin resistance is also increasing among viridans streptococci, with up to 49% of strains now resistant [19,25]. Published reports have confirmed the activity of third- and fourth-generation cephalosporins against these pathogens [26,39]. In one study, comparing the activity of ten cephalosporins against α-hemolytic streptococci recovered from blood, cefpirome was found to be the most active agent with an MIC_{90} of 1.0 mg/L, followed by cefazolin and cefotaxime, with MIC_{90} values of 2.0 mg/L [39].

Recent data showing the susceptibility of viridans streptococci to third- and fourth-generation cephalosporins and imipenem are shown in Table 4. For intermediate penicillin-resistant strains, cefpirome was again two-fold more active than cefotaxime in terms of the MIC_{90} value, and four-fold more active than cefepime. The MIC_{90} values of cefpirome, cefocelis, cefepime and cefotaxime against penicillin-resistant strains were 8 mg/L and imipenem was two-fold more active, with an MIC_{90} value of 4 mg/L.

Table 4 Susceptibility of viridans streptococci from Spain to five β-lactam antibiotics

Category	Antibiotic	MIC (mg/L)		
		50%	90%	Range
Penicillin-susceptible	ceftazidime[a]	1	2	0.12–4
(MIC < 0.25 mg/L)	cefepime	0.12	0.25	0.015–1.0
n = 272	cefpirome	0.03	0.12	0.015–0.25
	cefotaxime	0.06	0.25	0.015–0.25
	imipenem	0.015	0.06	0.015–0.06
Penicillin-intermediate	ceftazidime[a]	4	16	1.0–>32
(MIC 0.25–2.0 mg/L)	cefepime	0.25	2	0.015–2
n = 101	cefpirome	0.12	0.5	0.015–1.0
	cefotaxime	0.12	1.0	0.015–1.0
	imipenem	0.12	0.25	0.015–0.5
Penicillin-resistant	ceftazidime[a]	8	16	1.0–32
(MIC ≥ 4 mg/L)	cefepime	4	8	1.0–16
n = 37	cefpirome	2	8	0.12–8
	cefotaxime	2	8	0.5–16
	imipenem	1.0	4	0.12–8

[a]Only 120 strains were studied (70 sensitive, 25 intermediate-resistant and 25 highly-resistant).
Adapted from Alcaide et al. [25]. With permission of Am Soc Microbiol J Div.

Ceftazidime was also shown to have poor activity against viridans streptococci, with MIC_{90} values of 16 mg/L for penicillin-intermediate and penicillin-resistant strains. This may have clinical implications, as penicillin-resistant strains are being implicated more frequently in serious infections, particularly those caused by viridans streptococci in the neutropenic patient [13,14].

Bactericidal activity

Time-kill studies were performed against penicillin-susceptible, penicillin-intermediate and penicillin-resistant pneumococci and viridans streptococci. The bactericidal activity of cefpirome was compared with those of penicillin and cefotaxime at 2x and 4x the MIC values. Cefpirome showed the same degree of bactericidal activity as penicillin and cefotaxime against penicillin-susceptible, -intermediate and -resistant strains of *S. pneumoniae* (Table 5). These results confirm other published data [40], where a 3–4 $\log_{10}$ reduction in numbers of viable bacteria was achieved within 6 hours, for penicillin-intermediate and penicillin-resistant strains of *S. pneumoniae* treated with cefotaxime and cefpirome at 2x and 4x the MIC values. The rapid

Table 5 Bactericidal activities of penicillin, cefotaxime and cefpirome against penicillin-susceptible, -intermediate and -resistant *S. pneumoniae*

Strain	Antibiotic	MIC	Decrease in numbers of viable bacteria (log cfu/ml) from 0 h[a]			
			2 x MIC		4 x MIC	
		(mg/L)	3 h	6 h	3 h	6 h
32928	penicillin	0.03	4.43	≥ 4.80	4.43	≥ 4.80
	cefotaxime	0.03	4.23	≥ 4.80	4.43	≥ 4.80
	cefpirome	0.03	4.23	≥ 4.80	4.43	≥ 4.80
14901	penicillin	0.5	2.74	3.67	3.11	3.73
	cefotaxime	0.5	2.59	3.60	2.70	3.67
	cefpirome	0.25	2.59	3.50	2.62	3.53
14471	penicillin	4	2.55	3.52	3.00	3.52
	cefotaxime	4	2.89	3.65	3.00	3.62
	cefpirome	2	2.96	3.36	3.00	3.52

[a]Time-kill studies were performed in cation-supplemented Mueller Hinton broth + 2.5% lyzed horse blood. [Baquero, unpublished data].

bactericidal effect may play a role in the therapeutic response of pneumococci to these agents.

In contrast, in the case of the viridans streptococci, the bactericidal activity was very low for penicillin, cefpirome and cefotaxime against the penicillin-intermediate and penicillin-resistant strains, with only 1–2 $\log_{10}$ decreases being achieved by 6 hours at 4x the MIC values. This suggested that infections caused by these organisms may be refractory to monotherapy, particularly in the setting of endocarditis. All three compounds showed similar rates of bactericidal activity, however, the only difference seen was against the penicillin-susceptible strain, where the bactericidal effect of penicillin was slightly better than for the cephalosporins at 2x MIC.

Antibiotic combinations

For serious infections involving streptococci, a β-lactam, often in combination with another agent such as a glycopeptide or an aminoglycoside, may be used for empirical therapy. The activity of penicillin and cefpirome in combination with other agents was measured using chequerboard MIC determinations. The results show total and partial (or additive) synergistic interactions between penicillin or cefpirome and vancomycin, fosfomycin or gentamicin against 15 strains of intermediate and high-level penicillin-resistant strains of *S. pneumoniae* and viridans streptococci (Table 6). Synergy was calculated using fractional inhibitory concentrations (FICs) [41].

In general, against *S. pneumoniae*, vancomycin demonstrated a lower frequency of total synergistic interactions than fosfomycin or gentamicin when combined with penicillin, but 80% of the strains showed partial synergy. For fosfomycin, combined with penicillin or cefpirome, either partial or total synergy was seen against all the strains. A similar situation was seen for gentamicin in combination with penicillin, but, curiously, gentamicin plus cefpirome did not show such a high level of synergy as with penicillin (Table 6).

Despite only partial synergy being demonstrated between cefpirome and vancomycin in chequerboard MIC studies against penicillin-resistant pneumococci, time-kill studies against 9 strains of *S. pneumoniae* (3 penicillin-susceptible, 3 penicillin-intermediate and 3 penicillin-resistant) demonstrated synergistic interactions (synergy was defined as a ≥ 2 $\log_{10}$ decrease in viable count with the combination compared with the more active of each of the two compounds tested alone) (Table 7). The concentrations of cefpirome (1x MIC) and vancomycin (0.5x MIC) used showed little or no bactericidal activity when tested alone, but showed a decrease of at least 3 $\log_{10}$ in the numbers of viable bacteria by 6 hours when tested in combination, for all nine strains of *S. pneumoniae*.

In a further study conducted by Bajakouzian et al. [42], cefpirome and cefotaxime demonstrated synergistic or additive interactions with vancomycin and teicoplanin against penicillin-susceptible, -intermediate and -resistant pneumococci, using MIC chequerboard titration, with none of the combinations being antagonistic. In time-kill studies all four combinations demonstrated synergy against nine strains.

The same pattern of synergistic interactions was seen with the viridans streptococci (Table 6). Cefpirome was slightly less synergistic than penicillin with vancomycin, fosfomycin or gentamicin against the viridans streptococci; nevertheless, more than 50% of the strains showed either total or partial synergy for all the combinations tested.

Overall, these data suggest that there would be an advantage, in terms of antibacterial activity, in combining

Table 6 Strains of *S. pneumoniae* and viridans streptococci (penicillin-intermediate and -resistant) in which FIC[a] indices in chequerboard titration indicate drug synergism or additive activity

		% strains					
		Penicillin-vancomycin	Penicillin-fosfomycin	Penicillin-gentamicin	Cefpirome-vancomycin	Cefpirome-fosfomycin	Cefpirome-gentamicin
S. pneumoniae	Synergy	20	60	60	0	45	25
	Additive	80	100	95	95	100	50
Viridans streptococci	Synergy	30	60	65	10	40	20
	Additive	70	100	85	60	100	50

[a]The FICs were calculated as the MICs of both drugs in combination/the MIC for the drug alone, and the FIC index was obtained by adding the FICs. FIC indices were interpreted as synergistic if the values were ≤ 0.5, partial or additive if the values were > 0.5–1.0, and antagonistic if the values were > 1.0. [Baquero, unpublished data].

Table 7 Bactericidal activities of cefpirome and vancomycin, alone and in combination, against nine strains of *S. pneumoniae*

Strain	Change in $\log_{10}$ bacterial colony count from 0 h[a]					
	4 h			6 h		
	Cefpirome[b]	Vancomycin[c]	Cefpirome[b] + vancomycin[c]	Cefpirome[b]	Vancomycin[c]	Cefpirome[b] + vancomycin[c]
S13	- 0.89	+ 0.11	- 3.48	- 0.23	+ 0.62	- 4.56
S32	+ 0.74	- 0.50	- 3.73	+ 0.81	+ 1.05	- 4.30
S40	+ 0.66	+ 1.53	- 3.24	+ 0.79	+ 1.61	- 3.70
110	+ 0.55	+ 0.33	- 4.62	+ 1.31	+ 2.21	- 5.18
141	- 0.43	+ 0.32	- 3.62	- 1.76	+ 0.40	- 3.98
1145	+ 0.18	+ 0.46	- 2.37	+ 0.93	+ 1.79	- 4.00
R11	+ 0.27	+ 0.82	- 2.73	+ 2.15	+ 1.92	- 4.57
R13	+ 1.37	+ 2.39	- 4.29	+ 1.70	+ 2.94	- 4.53
R14	- 0.18	+ 0.33	- 2.55	+ 1.67	+ 1.80	-5.00
Mean ± SD	+0.25 ± 0.64	+0.64 ± 0.8	-3.4 ± 0.72	+0.82 ± 1.12	+1.59 ± 0.75	-4.42 ± 0.46

[a]Time-kill studies were performed in cation-supplemented Mueller Hinton broth + 2.5% lyzed horse blood.
[b]Cefpirome was tested at 1 x MIC.
[c]Vancomycin was tested at 0.25 mg/L (0.5 x MIC for all strains).

a β-lactam antibiotic (penicillin or cefpirome) with another agent (glycopeptide, fosfomycin or gentamicin) when treating some infections caused by penicillin-resistant streptococci, although this needs to be confirmed by in vivo and clinical studies.

CLINICAL IMPLICATIONS

Many strains of pneumococci are multidrug-resistant and strains with resistance to the third-generation cephalosporins are being reported [21,43]. The appropriate antibiotic therapy for pneumococcal infections due to resistant strains still remains controversial. In an attempt to address this problem, the relationship between in vitro data and clinical outcome must be considered. Selection of antibiotics should be made on the basis of the site of infection, the need for bactericidal activity and the pharmacodynamic properties of the compound [44].

Pneumococcal pneumonia

The results of a 10-year prospective study of 504 patients with bacteriologically-proven pneumococcal pneumonia were reported in 1995 [45]. Of these, 29% were infected with penicillin-resistant strains (penicillin MIC values, 0.12–4 mg/L) and 6% had cephalosporin-resistant strains (cefotaxime MIC values, 1–4 mg/L). Although differences were found in the mortality rate in nosocomial pneumonia caused by penicillin-resistant (38% mortality) and penicillin-susceptible (24% mortality) strains of *S. pneumoniae*, when the data were adjusted to take into account polymicrobial infections and the type of underlying illness, there was no difference between the two groups. Amongst patients treated with ampicillin or penicillin G, the mortality rate was 25% in patients with penicillin-resistant strains and 19% in patients with penicillin-susceptible strains and, amongst patients treated with ceftriaxone or cefotaxime, the mortality rate was 22% for penicillin-resistant strains and 25% for penicillin-susceptible strains. Furthermore, for patients treated with cefotaxime or ceftriaxone, the mortality rate was 22% for cephalosporin-resistant *S. pneumoniae* and 24% for cephalosporin-sensitive strains.

Another study [46], also demonstrated no difference in the mortality rate in children with pneumococcal bacteremia caused by penicillin-resistant strains of pneumococci (14%), compared with that seen in children infected with penicillin-susceptible strains (11%). More recent data show that there was no difference in time to resolution of signs and symptoms, and the clinical course was similar, for intravenous penicillin or ampicillin therapy of penicillin-resistant and penicillin-sensitive pneumococcal pneumonia in children [47]. Similar observations were seen in patients treated for pneumonia caused by strains of pneumococci which were resistant in vitro to cefuroxime but responded clinically [48,49].

These data suggest that penicillin MIC values are not the primary determinant predicting the clinical outcome of pneumococcal pneumonia, at least up to an MIC value of 4 mg/L. In order to examine the response of penicillin-susceptible and penicillin-resistant pneumococci to treatment with penicillin in more detail, Figure 2 shows a peritonitis mouse model used to determine the 50% effective dose (ED_{50}) of

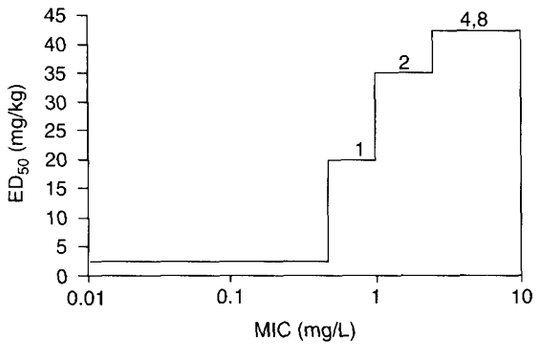

Figure 2 Effect of increasing the MIC values of penicillin on the 50% effective dose (ED_{50}) in a *S. pneumoniae* peritonitis mouse model following penicillin treatment. From Knudsen et al. [50]. With permission of Am Soc Microbiol J Div.

penicillin against strains of *S. pneumoniae* with different penicillin MIC values [50]. There was little difference in the ED_{50} of penicillin in mice infected with strains with MIC values ranging from 0.016–0.5 mg/L. For strains with higher MIC values (> 1 mg/L), however, the ED_{50} increased in a stepwise fashion. This continued up to an MIC value of 4 mg/L, following which the ED_{50} levelled out at around 45 mg/kg. This means that small differences in MIC could be crucial in determining the clinical outcome, particularly in certain infections. In pneumonia, the concentrations of antibiotic achieved at the site of infection are probably high enough to cope with strains with MIC values up to 4 mg/L, so no difference in efficacy would be seen for strains with MIC values of 0.1–4 mg/L [45].

For patients in whom suspected pneumococcal pneumonia is caused by highly-resistant strains and, in addition, an underlying immunodeficiency, an alternative regimen would be to use third- or fourth-generation cephalosporins with enhanced activity against these strains or a carbapenem [51]. The bactericidal activity of β-lactams is concentration-independent and time above MIC correlates most closely with clinical outcome [44]. If the maximum concentrations of cefpirome achieved in serum are examined for standard dosage; the peak serum concentration after an intravenous injection of 2 g is 173 mg/L [52], whereas that for a 1 g dose is 81 mg/L. The half-life of cefpirome is 2 hours so that, for the 2 g intravenous dose, the serum concentration of cefpirome exceeds the maximum MIC value observed against penicillin-resistant pneumococci (penicillin MIC 4 mg/L; cefpirome MIC 1 mg/L) for the whole 12-hour dosing interval. This concentration is exceeded for around 10 hours following a 1 g intravenous dose and for the whole 12-hour dosing interval following administration of a 1 g intramuscular dose, although the serum peak was only 22 mg/L in the latter case [52]. The maximum MIC value against penicillin-intermediate strains of viridans streptococci is 1.0 mg/L and these strains are therefore well covered by concentrations of cefpirome achieved in serum, whereas the maximum MIC value against penicillin-resistant strains (8 mg/L) is exceeded in serum for 6–8 hours following intravenous or intramuscular dosage of 2 g cefpirome. This time above MIC of 50–67% of the dosing interval may be sufficient for clinical efficacy, although this is questionable for neutropenic patients, and needs to be investigated using in vivo models or clinical studies. It is also important to stress that current resistance levels may increase and recommended dosage levels and regimens may have to be increased likewise. Alternatively, combination therapy could be considered. The results of in vitro synergy studies suggest that a combination of a β-lactam with an aminoglycoside should be the treatment of choice against penicillin-resistant viridans streptococcal endocarditis, and this needs to be confirmed clinically.

Meningitis

At present, the third-generation cephalosporins, cefotaxime and ceftriaxone, are the preferred antibiotics for initial empiric therapy for suspected pneumococcal meningitis. Most penicillin-resistant strains are inhibited by a maximum MIC of 2 mg/L. Failure of cephalosporin treatment is increasingly reported with strains having MIC values of ≥ 2 mg/L and cefotaxime or ceftriaxone should not be used alone to treat resistant cases [51]. For resistant strains, vancomycin or rifampicin should be used in addition to the third-generation cephalosporin. An alternative could be the use of new classes of antibiotic such as the carbapenems or the fourth-generation cephalosporins. Meropenem has been used to treat a large number of children with meningitis, but more data are required on the treatment of penicillin-resistant strains [53]. Clinical trials are also needed to support the use of the fourth-generation cephalosporins in this indication.

In meningitis, it is the concentration of antibiotic in the cerebrospinal fluid (CSF) which is important in determining clinical outcome. In an experimental pneumococcal meningitis infection in rabbits, the fourth-generation cephalosporins, cefpirome and cefepime demonstrated good penetration into CSF compared to cefotaxime [54]. Following intravenous infusion of cefepime at 25 mg/kg/h and cefpirome at 10 mg/kg/h, 9.6 and 6.6 mg/L, respectively were achieved in the CSF, indicating 16.2% and 19.3% penetration. In contrast, cefotaxime attained only

2.3 mg/L following a 50 mg/kg/h intravenous infusion, indicating 4.3% penetration. In another pneumococcal meningitis rabbit model [55], the efficacy of several agents and combinations were compared against penicillin-sensitive and -resistant strains. This study confirmed the excellent CSF penetration of cefpirome compared to meropenem, rifampicin and vancomycin.

A further study found mean peak CSF concentrations of cefpirome of 4 mg/L, obtained 4 hours after an intravenous dose of 2 g cefpirome, in adult patients with purulent meningitis [56]. A more recent study, in which children were administered 300 mg/kg cefotaxime, showed mean levels of 4–5 mg cefotaxime/L in CSF, with wide variability, such that some patients had levels below 1.0 mg/L [Friedland, Klugman, personal communication]. Preliminary studies with cefpirome in children suggest that the penetration of cefpirome into CSF is better than that of cefotaxime [Friedland, unpublished data]. The concentration of cefpirome reported in the CSF of adults with purulent meningitis [56] exceeded the maximum MIC value of cefpirome against penicillin-resistant *S. pneumoniae* and penicillin-intermediate viridans streptococci (1.0 mg/L) for the whole 12-hour dosing interval.

Other experimental drugs, such as the new quinolones (sparfloxacin, clinafloxacin, grepafloxacin, levofloxacin, trovafloxacin), oral and parenteral streptogrammins (quinupristin/dalfopristin) and the oxazolidinones (U-100572, U-100766), have shown promising activity in vitro against penicillin-resistant pneumococci. The therapeutic usefulness of these agents must await toxicological, pharmacokinetic and clinical studies [19,43].

SUMMARY

The incidence of penicillin resistance amongst *S. pneumoniae* is increasing at such a rapid rate that we are currently facing a pandemic situation. Many penicillin-resistant pneumococci are multiresistant, precluding the use of alternative agents, such as the macrolides, tetracyclines and chloramphenicol [6–10]. The treatment of choice for most pneumococcal infections remains a β-lactam antibiotic. Fourth-generation cephalosporins, such as cefpirome, have shown potent activity against penicillin-resistant pneumococci, being more active than cefotaxime and ceftriaxone, the current β-lactam agents of choice.

The antibiotic management of meningitis, in particular, has been complicated by the emergence of penicillin- and cephalosporin-resistant strains. The third-generation cephalosporins (cefotaxime and ceftriaxone) are now the empirical drugs of choice for the management of pneumococcal meningitis. For resistant strains, a glycopeptide or rifampicin should be added to the regimen. An alternative to this could be the use of new classes such as the carbapenems or fourth-generation cephalosporins, although more clinical data are needed.

Viridans streptococci have also acquired penicillin resistance [15–17], via the same mechanism as *S. pneumoniae* [30] and, although there are less epidemiological data for this group of organisms, they are increasingly being implicated in serious infections, such as meningitis and bacteremia, particularly in neutropenic patients. Penicillin-resistant viridans streptococci are potentially a much greater problem as they are less susceptible, and show tolerance to all the β-lactam antibiotics tested.

The current MIC breakpoints for susceptibility to β-lactam antibiotics may need to be modified, to reflect recent clinical data. For instance, in pneumonia or bacteremia, streptococci up to a certain level of penicillin resistance will respond to conventional β-lactam therapy, but in the case of infections in closed compartments, such as meningitis or otitis media, a lower breakpoint may be required.

DISCUSSION

Prof. M. Glauser: Regarding the map which illustrates the world-wide distribution of intermediate and penicillin-resistant pneumococci, are data available regarding the corresponding figures for high level penicillin-resistant pneumococci, as these organisms are the most important in the clinical situation?

Prof. F. Baquero: The number of countries represented will be extremely low, as there are very few data available concerning high-level penicillin resistance, and this will differ from country to country. In most southern European countries, such as Spain, Portugal or France, the rate of high-level resistance among the total number of strains is approximately 33%. In some other countries such as Germany, the rate of penicillin-resistant pneumococci is 10%, although these are mainly intermediately penicillin-resistant strains.

Prof. K. Klugman: In countries with a low rate of penicillin resistance, most of the strains will be intermediately penicillin-resistant. South Africa is an exception, as a problem with penicillin resistance (intermediate and high-level) has been in existence for many years; there is also a wide diversity of clones. However, the actual incidence of high-level penicillin resistance is quite low in South Africa. Unfortunately,

in most of the parts of the world where resistance is rapidly developing, such as South America, Australia, Western Europe and the USA, approximately a third of strains are highly penicillin-resistant.

Prof. M. Glauser: Are there more data regarding the incidence of penicillin resistance among viridans group streptococci?

Prof. F. Baquero: There are currently only limited data available and for countries where data has been published, the rate of penicillin resistance is high. For instance, in Spain the rate of penicillin resistance is nearly 30% and in the USA and South Africa the rate is nearly 40%.

It would be valuable to obtain data for France and to compare the rates of penicillin resistance among pneumococci and viridans group streptococci, as there is some evidence that viridans streptococci acquired penicillin resistance before the pneumococci.

Prof. W. Wilson: Dr G. Doern from the NCCLS has proposed a lower breakpoint for penicillin against viridans group streptococci than for the cephalosporins. This means that the penicillin-intermediate range of 0.25–2 mg/L is quite high for penicillin susceptibility for viridans streptococci.

Prof. F. Baquero: In terms of PBP alterations and the MIC distribution profile, the current susceptibility breakpoints are still applicable but they may not be clinically relevant.

Prof. K. Klugman: In our experience ceftriaxone is still effective, at least in combination, in treating endocarditis caused by viridans streptococci. However, it is not known to what extent highly penicillin-resistant strains are involved.

Prof. P. Francioli: One hundred cases of endocarditis have been treated using a 2 g dose of ceftriaxone, although only a very few patients had strains with MICs > 0.25 mg/L. An alternative regimen would be combining ceftriaxone with an aminoglycoside, particularly for strains with MICs > 0.5 mg/L.

Prof. W. Wilson: Over a 35 year period at the Mayo Clinic, approximately a third of patients with endocarditis had tolerant viridans streptococci and 4% had intermediately penicillin-resistant viridans streptococci (i.e. MIC > 0.5 mg/L). All patients were treated successfully with combination therapy of penicillin plus an aminoglycoside, even patients with susceptible organisms. In animal infection models, data have shown that strains with increased penicillin resistance did not respond as well to monotherapy compared with the fully susceptible strains. The American HEART statement published in JAMA about eight months ago suggested that combination therapy for the first two weeks of a four week regimen was recommended for strains with MICs, 0.1–0.5 mg/L. For strains with MICs > 0.5mg/L it was suggested that therapy should be similar to that for enterococcal endocarditis.

Prof. K. Klugman: In meningitis, there is wide variation in the CSF penetration of cefotaxime. The penetration is insufficient to cover strains with MICs of ≥ 2 mg/L, even when using a higher dose of cefotaxime (300 mg/kg/day). In these cases combination therapy with vancomycin is recommended. Clinical studies with compounds such as cefpirome as monotherapy warrant further investigation.

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